

**ALUNBRIG- brigatinib tablet, coated**  
**ARIAD Pharmaceuticals Inc.**

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use ALUNBRIG safely and effectively. See full prescribing information for ALUNBRIG.

**ALUNBRIG™ (brigatinib) tablets, for oral use**

**Initial U.S. Approval: 2017**

----- **INDICATIONS AND USAGE** -----

ALUNBRIG is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. (1)

----- **DOSAGE AND ADMINISTRATION** -----

90 mg orally once daily for the first 7 days; if tolerated, increase to 180 mg orally once daily. May be taken with or without food. (2.1)

----- **DOSAGE FORMS AND STRENGTHS** -----

Tablets: 30 mg and 90 mg (3)

----- **CONTRAINDICATIONS** -----

None. (4)

----- **WARNINGS AND PRECAUTIONS** -----

- **Interstitial Lung Disease (ILD)/Pneumonitis:** Occurred in 9.1% of patients at the recommended dose. Monitor for new or worsening respiratory symptoms, particularly during the first week of treatment. Withhold ALUNBRIG for new or worsening respiratory symptoms and promptly evaluate for ILD/pneumonitis. Upon recovery, either dose reduce or permanently discontinue ALUNBRIG. (2.2, 5.1)
- **Hypertension:** Monitor blood pressure after 2 weeks and then at least monthly during treatment. For severe hypertension, withhold ALUNBRIG, then dose reduce or permanently discontinue. (2.2, 5.2)
- **Bradycardia:** Monitor heart rate and blood pressure regularly during treatment. If symptomatic, withhold ALUNBRIG, then dose reduce or permanently discontinue. (2.2, 5.3)
- **Visual Disturbance:** Advise patients to report visual symptoms. Withhold ALUNBRIG and obtain ophthalmologic evaluation, then dose reduce or permanently discontinue ALUNBRIG. (2.2, 5.4)
- **Creatine Phosphokinase (CPK) Elevation:** Monitor CPK levels regularly during treatment. Based on the severity, withhold ALUNBRIG, then resume or reduce dose. (2.2, 5.5)
- **Pancreatic Enzyme Elevation:** Monitor lipase and amylase levels regularly during treatment. Based on the severity, withhold ALUNBRIG, then resume or reduce dose. (2.2, 5.6)
- **Hyperglycemia:** Assess fasting serum glucose prior to starting ALUNBRIG and regularly during treatment. If not adequately controlled with optimal medical management, withhold ALUNBRIG, then consider dose reduction or permanently discontinue, based on severity. (2.2, 5.7)
- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use a non-hormonal method of effective contraception. (5.8, 8.1, 8.3)

----- **ADVERSE REACTIONS** -----

The most common adverse reactions (≥25%) with ALUNBRIG were nausea, diarrhea, fatigue, cough, and headache. (6)

**To report SUSPECTED ADVERSE REACTIONS, contact ARIAD Pharmaceuticals, Inc. at 1-844-217-6468 or [www.alunbrig.com](http://www.alunbrig.com) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

----- **DRUG INTERACTIONS** -----

- **CYP3A Inhibitors:** Avoid concomitant use of ALUNBRIG with strong CYP3A inhibitors. If concomitant use of a strong CYP3A inhibitor is unavoidable, reduce the dose of ALUNBRIG. (2.3, 7.1)
- **CYP3A Inducers:** Avoid concomitant use of ALUNBRIG with strong CYP3A inducers. (7.2)
- **CYP3A Substrates:** Hormonal contraceptives may be ineffective due to decreased exposure. (7.3)

----- **USE IN SPECIFIC POPULATIONS** -----

Lactation: Advise not to breastfeed. (8.2)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

**Revised: 4/2017**

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## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

ALUNBRIG is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. This indication is approved under accelerated approval based on tumor response rate and duration of response [see *Clinical Studies (14)*]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dosing

The recommended dosing regimen for ALUNBRIG is:

- 90 mg orally once daily for the first 7 days;
- if 90 mg is tolerated during the first 7 days, increase the dose to 180 mg orally once daily.

Administer ALUNBRIG until disease progression or unacceptable toxicity.

If ALUNBRIG is interrupted for 14 days or longer for reasons other than adverse reactions, resume treatment at 90 mg once daily for 7 days before increasing to the previously tolerated dose.

ALUNBRIG may be taken with or without food. Instruct patients to swallow tablets whole. Do not crush or chew tablets.

If a dose of ALUNBRIG is missed or vomiting occurs after taking a dose, do not administer an additional dose and take the next dose of ALUNBRIG at the scheduled time.

### 2.2 Dose Modifications for Adverse Reactions

ALUNBRIG dose modification levels are summarized in Table 1.

**Table 1: Recommended ALUNBRIG Dose Reduction Levels**

Dose	Dose Reduction Levels		
	First	Second	Third
90 mg once daily	60 mg once daily	permanently discontinue	N/A *
180 mg once daily	120 mg once daily	90 mg once daily	60 mg once daily

\* Not applicable

Once reduced for adverse reactions, do not subsequently increase the dose of ALUNBRIG. Permanently discontinue ALUNBRIG if patients are unable to tolerate the 60 mg once daily dose.

Recommendations for dose modifications of ALUNBRIG for the management of adverse reactions are provided in Table 2.

**Table 2: Recommended ALUNBRIG Dose Modifications for Adverse Reactions**

Adverse Reaction	Severity*	Dose Modification
	Grade 1	<ul style="list-style-type: none"> <li>• If new pulmonary symptoms occur <u>during</u> the first 7 days of treatment, withhold ALUNBRIG until recovery to baseline, then resume at same dose and do not escalate to 180 mg if ILD/pneumonitis is suspected.</li> <li>• If new pulmonary symptoms occur <u>after</u> the first 7 days of treatment, withhold ALUNBRIG until recovery to baseline, then resume at same dose.</li> <li>• If ILD/pneumonitis recurs, permanently</li> </ul>

Interstitial Lung Disease (ILD) /Pneumonitis [see Warnings and Precautions (5.1)]		discontinue ALUNBRIG.
	Grade 2	<ul style="list-style-type: none"> <li>• If new pulmonary symptoms occur <u>during</u> the first 7 days of treatment, withhold ALUNBRIG until recovery to baseline. Resume at next lower dose (Table 1) and do not dose escalate if ILD/pneumonitis is suspected.</li> <li>• If new pulmonary symptoms occur <u>after</u> the first 7 days of treatment, withhold ALUNBRIG until recovery to baseline. If ILD/pneumonitis is suspected, resume at next lower dose (Table 1); otherwise, resume at same dose.</li> <li>• If ILD/pneumonitis recurs, permanently discontinue ALUNBRIG.</li> </ul>
	Grade 3 or 4	Permanently discontinue ALUNBRIG for ILD/pneumonitis.
Hypertension [see Warnings and Precautions (5.2)]	Grade 3 hypertension (SBP greater than or equal to 160 mmHg or DBP greater than or equal to 100 mmHg, medical intervention indicated, more than one anti-hypertensive drug, or more intensive therapy than previously used indicated)	<ul style="list-style-type: none"> <li>• Withhold ALUNBRIG until hypertension has recovered to Grade 1 or less (SBP less than 140 mmHg and DBP less than 90 mmHg), then resume ALUNBRIG at next lower dose (Table 1).</li> <li>• Recurrence: withhold ALUNBRIG until recovery to Grade 1 or less, and resume at next lower dose (Table 1) <u>or</u> permanently discontinue treatment.</li> </ul>
	Grade 4 hypertension (life-threatening consequences, urgent intervention indicated)	<ul style="list-style-type: none"> <li>• Withhold ALUNBRIG until recovery to Grade 1 or less, and resume at next lower dose (Table 1) <u>or</u> permanently discontinue treatment.</li> <li>• Recurrence: permanently discontinue ALUNBRIG for recurrence of Grade 4 hypertension.</li> </ul>
Bradycardia (HR less than 60 bpm) [see Warnings and Precautions (5.3)]	Symptomatic bradycardia	<ul style="list-style-type: none"> <li>• Withhold ALUNBRIG until recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above.</li> <li>• If a concomitant medication known to cause bradycardia is identified and discontinued or dose-adjusted, resume ALUNBRIG at same dose upon recovery to asymptomatic bradycardia or to resting heart rate of 60 bpm or above.</li> <li>• If no concomitant medication known to cause bradycardia is identified, or if contributing concomitant medications are not discontinued or dose-adjusted, resume ALUNBRIG at next lower dose (Table 1) upon recovery to asymptomatic bradycardia or to resting heart rate of 60 bpm or above.</li> </ul>
		<ul style="list-style-type: none"> <li>• Permanently discontinue ALUNBRIG if no</li> </ul>

	Bradycardia with life-threatening consequences, urgent intervention indicated	<p>contributing concomitant medication is identified.</p> <ul style="list-style-type: none"> <li>• If contributing concomitant medication is identified and discontinued or dose-adjusted, resume ALUNBRIG at next lower dose (Table 1) upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above, with frequent monitoring as clinically indicated.</li> <li>• Recurrence: permanently discontinue ALUNBRIG.</li> </ul>
Visual Disturbance <i>[see Warnings and Precautions (5.4)]</i>	Grade 2 or 3 visual disturbance	Withhold ALUNBRIG until recovery to Grade 1 or baseline, then resume at the next lower dose (Table 1).
	Grade 4 visual disturbance	Permanently discontinue ALUNBRIG.
Creatine Phosphokinase (CPK) Elevation <i>[see Warnings and Precautions (5.5)]</i>	Grade 3 CPK elevation (greater than $5.0 \times \text{ULN}$ )	Withhold ALUNBRIG until recovery to Grade 1 or less (less than or equal to $2.5 \times \text{ULN}$ ) or to baseline, then resume ALUNBRIG at same dose.
	Grade 4 CPK elevation (greater than $10.0 \times \text{ULN}$ ) or recurrence of Grade 3 elevation	Withhold ALUNBRIG until recovery to Grade 1 or less (less than or equal to $2.5 \times \text{ULN}$ ) or to baseline, then resume ALUNBRIG at next lower dose (Table 1).
Lipase/Amylase Elevation <i>[see Warnings and Precautions (5.6)]</i>	Grade 3 lipase or amylase elevation (greater than $2.0 \times \text{ULN}$ )	Withhold ALUNBRIG until recovery to Grade 1 or less (less than or equal to $1.5 \times \text{ULN}$ ) or to baseline, then resume ALUNBRIG at same dose.
	Grade 4 lipase or amylase elevation (greater than $5.0 \times \text{ULN}$ ) or recurrence of Grade 3 elevation	Withhold ALUNBRIG until recovery to Grade 1 or less (less than or equal to $1.5 \times \text{ULN}$ ) or to baseline, then resume ALUNBRIG at next lower dose (Table 1).
Hyperglycemia <i>[see Warnings and Precautions (5.7)]</i>	Grade 3 (greater than 250 mg/dL or 13.9 mmol/L) or greater	If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold ALUNBRIG until adequate hyperglycemic control is achieved and consider reduction to the next dose (Table 1) <u>or</u> permanently discontinue ALUNBRIG.
Other	Grade 3	<ul style="list-style-type: none"> <li>• Withhold ALUNBRIG until recovery to baseline, then resume at same dose.</li> <li>• Recurrence: withhold ALUNBRIG until recovery to baseline, then resume at next lower dose or discontinue ALUNBRIG (Table 1).</li> </ul>
	Grade 4	<ul style="list-style-type: none"> <li>• First occurrence: either withhold ALUNBRIG until recovery to baseline and resume at next lower dose (Table 1) <u>or</u> permanently discontinue.</li> <li>• Permanently discontinue ALUNBRIG for recurrence.</li> </ul>

bpm = beats per minute; DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure; ULN = upper limit of normal

\* Graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4).

## 2.3 Dose Modification for Strong CYP3A Inhibitors

Avoid concomitant use of strong CYP3A inhibitors during treatment with ALUNBRIG [see *Drug Interactions (7.1) and Clinical Pharmacology (12.3)*]. If concomitant use of a strong CYP3A inhibitor cannot be avoided, reduce the ALUNBRIG once daily dose by approximately 50% (i.e., from 180 mg to 90 mg, or from 90 mg to 60 mg). After discontinuation of a strong CYP3A inhibitor, resume the ALUNBRIG dose that was tolerated prior to initiating the strong CYP3A inhibitor.

## 3 DOSAGE FORMS AND STRENGTHS

- 30 mg, round, white to off-white film-coated tablet with "U3" debossed on one side and plain on the other side
- 90 mg, oval, white to off-white film-coated tablet with "U7" debossed on one side and plain on the other side

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Interstitial Lung Disease (ILD)/Pneumonitis

Severe, life-threatening, and fatal pulmonary adverse reactions consistent with interstitial lung disease (ILD)/pneumonitis have occurred with ALUNBRIG.

In Trial ALTA (ALTA), ILD/pneumonitis occurred in 3.7% of patients in the 90 mg group (90 mg once daily) and 9.1% of patients in the 90 → 180 mg group (180 mg once daily with 7-day lead-in at 90 mg once daily).

Adverse reactions consistent with possible ILD/pneumonitis occurred early (within 9 days of initiation of ALUNBRIG; median onset was 2 days) in 6.4% of patients, with Grade 3 to 4 reactions occurring in 2.7%.

Monitor for new or worsening respiratory symptoms (e.g., dyspnea, cough, etc.), particularly during the first week of initiating ALUNBRIG. Withhold ALUNBRIG in any patient with new or worsening respiratory symptoms, and promptly evaluate for ILD/pneumonitis or other causes of respiratory symptoms (e.g., pulmonary embolism, tumor progression, and infectious pneumonia). For Grade 1 or 2 ILD/pneumonitis, either resume ALUNBRIG with dose reduction according to Table 1 after recovery to baseline or permanently discontinue ALUNBRIG. Permanently discontinue ALUNBRIG for Grade 3 or 4 ILD/pneumonitis or recurrence of Grade 1 or 2 ILD/pneumonitis [see *Dosage and Administration (2.2) and Adverse Reactions (6.1)*].

### 5.2 Hypertension

In ALTA, hypertension was reported in 11% of patients in the 90 mg group who received ALUNBRIG and 21% of patients in the 90 → 180 mg group. Grade 3 hypertension occurred in 5.9% of patients overall.

Control blood pressure prior to treatment with ALUNBRIG. Monitor blood pressure after 2 weeks and at least monthly thereafter during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 hypertension despite optimal antihypertensive therapy. Upon resolution or improvement to Grade 1 severity, resume ALUNBRIG at a reduced dose. Consider permanent discontinuation of treatment with ALUNBRIG for Grade 4 hypertension or recurrence of Grade 3 hypertension [see *Dosage and Administration (2.2) and Adverse Reactions (6.1)*].

Use caution when administering ALUNBRIG in combination with antihypertensive agents that cause bradycardia [see *Warnings and Precautions* (5.3)].

### 5.3 Bradycardia

Bradycardia can occur with ALUNBRIG. In ALTA, heart rates less than 50 beats per minute (bpm) occurred in 5.7% of patients in the 90 mg group and 7.6% of patients in the 90 → 180 mg group. Grade 2 bradycardia occurred in 1 (0.9%) patient in the 90 mg group.

Monitor heart rate and blood pressure during treatment with ALUNBRIG. Monitor patients more frequently if concomitant use of drug known to cause bradycardia cannot be avoided [see *Warnings and Precautions* (5.2)].

For symptomatic bradycardia, withhold ALUNBRIG and review concomitant medications for those known to cause bradycardia. If a concomitant medication known to cause bradycardia is identified and discontinued or dose adjusted, resume ALUNBRIG at the same dose following resolution of symptomatic bradycardia; otherwise, reduce the dose of ALUNBRIG following resolution of symptomatic bradycardia. Discontinue ALUNBRIG for life-threatening bradycardia if no contributing concomitant medication is identified [see *Dosage and Administration* (2.2)].

### 5.4 Visual Disturbance

In ALTA, adverse reactions leading to visual disturbance including blurred vision, diplopia, and reduced visual acuity, were reported in 7.3% of patients receiving ALUNBRIG in the 90 mg group and 10% of patients in the 90 → 180 mg group. Grade 3 macular edema and cataract occurred in one patient each in the 90 → 180 mg group.

Advise patients to report any visual symptoms. Withhold ALUNBRIG and obtain an ophthalmologic evaluation in patients with new or worsening visual symptoms of Grade 2 or greater severity. Upon recovery of Grade 2 or Grade 3 visual disturbances to Grade 1 severity or baseline, resume ALUNBRIG at a reduced dose. Permanently discontinue treatment with ALUNBRIG for Grade 4 visual disturbances [see *Dosage and Administration* (2.2) and *Adverse Reactions* (6.1)].

### 5.5 Creatine Phosphokinase (CPK) Elevation

In ALTA, creatine phosphokinase (CPK) elevation occurred in 27% of patients receiving ALUNBRIG in the 90 mg group and 48% of patients in the 90 mg → 180 mg group. The incidence of Grade 3-4 CPK elevation was 2.8% in the 90 mg group and 12% in the 90 → 180 mg group.

Dose reduction for CPK elevation occurred in 1.8% of patients in the 90 mg group and 4.5% in the 90 → 180 mg group.

Advise patients to report any unexplained muscle pain, tenderness, or weakness. Monitor CPK levels during ALUNBRIG treatment. Withhold ALUNBRIG for Grade 3 or 4 CPK elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose as described in Table 2 [see *Dosage and Administration* (2.2) and *Adverse Reactions* (6.1)].

### 5.6 Pancreatic Enzyme Elevation

In ALTA, amylase elevation occurred in 27% of patients in the 90 mg group and 39% of patients in the 90 → 180 mg group. Lipase elevations occurred in 21% of patients in the 90 mg group and 45% of patients in the 90 → 180 mg group. Grade 3 or 4 amylase elevation occurred in 3.7% of patients in the 90 mg group and 2.7% of patients in the 90 → 180 mg group. Grade 3 or 4 lipase elevation occurred in 4.6% of patients in the 90 mg group and 5.5% of patients in the 90 → 180 mg group.

Monitor lipase and amylase during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 or 4 pancreatic enzyme elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose as described in Table 2 [see *Dosage and Administration* (2.2) and *Adverse Reactions* (6.1)].

## 5.7 Hyperglycemia

In ALTA, 43% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia, based on laboratory assessment of serum fasting glucose levels, occurred in 3.7% of patients. Two of 20 (10%) patients with diabetes or glucose intolerance at baseline required initiation of insulin while receiving ALUNBRIG.

Assess fasting serum glucose prior to initiation of ALUNBRIG and monitor periodically thereafter. Initiate or optimize anti-hyperglycemic medications as needed. If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold ALUNBRIG until adequate hyperglycemic control is achieved and consider reducing the dose of ALUNBRIG as described in Table 1 or permanently discontinuing ALUNBRIG [see *Dosage and Administration (2.2)* and *Adverse Reactions (6.1)*].

## 5.8 Embryo-Fetal Toxicity

Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to pregnant women. There are no clinical data on the use of ALUNBRIG in pregnant women. Administration of brigatinib to pregnant rats during the period of organogenesis resulted in dose-related skeletal anomalies at doses as low as 12.5 mg/kg/day (approximately 0.7 times the human exposure by AUC at 180 mg once daily) as well as increased post implantation loss, malformations, and decreased fetal body weight at doses of 25 mg/kg/day (approximately 1.26 times the human exposure at 180 mg once daily) or higher.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for at least 3 months after the last dose of ALUNBRIG [see *Use in Specific Populations (8.1 and 8.3)* and *Clinical Pharmacology (12.1)*].

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the prescribing information:

- Interstitial Lung Disease (ILD)/Pneumonitis [see *Warnings and Precautions (5.1)*]
- Hypertension [see *Warnings and Precautions (5.2)*]
- Bradycardia [see *Warnings and Precautions (5.3)*]
- Visual Disturbance [see *Warnings and Precautions (5.4)*]
- Creatine Phosphokinase (CPK) Elevation [see *Warnings and Precautions (5.5)*]
- Pancreatic Enzyme Elevation [see *Warnings and Precautions (5.6)*]
- Hyperglycemia [see *Warnings and Precautions (5.7)*]

### 6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of ALUNBRIG was evaluated in 219 patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) who received at least one dose of ALUNBRIG in ALTA after experiencing disease progression on crizotinib. Patients received ALUNBRIG 90 mg once daily continuously (90 mg group) or 90 mg once daily for 7 days followed by 180 mg once daily (90 → 180 mg group). The median duration of treatment was 7.5 months in the 90 mg group and 7.8 months in the 90 → 180 mg group. A total of 150 (68%) patients were exposed to ALUNBRIG for greater than or equal to 6 months and 42 (19%) patients were exposed for greater than or equal to one year.



The study population characteristics were: median age 54 years (range: 18 to 82), age less than 65 years (77%), female (57%), White (67%), Asian (31%), Stage IV disease (98%), NSCLC adenocarcinoma histology (97%), never or former smoker (95%), ECOG Performance Status (PS) 0 or 1 (93%), and brain metastases at baseline (69%) [see *Clinical Studies* (14)].

Serious adverse reactions occurred in 38% of patients in the 90 mg group and 40% of patients in the 90 → 180 mg group. The most common serious adverse reactions were pneumonia (5.5% overall, 3.7% in the 90 mg group, and 7.3% in the 90 → 180 mg group) and ILD/pneumonitis (4.6% overall, 1.8% in the 90 mg group and 7.3% in the 90 → 180 mg group). Fatal adverse reactions occurred in 3.7% of patients and consisted of pneumonia (2 patients), sudden death, dyspnea, respiratory failure, pulmonary embolism, bacterial meningitis and urosepsis (1 patient each).

In ALTA, 2.8% of patients in the 90 mg group and 8.2% of patients in the 90 → 180 mg group permanently discontinued ALUNBRIG for adverse reactions. The most frequent adverse reactions that led to discontinuation were ILD/pneumonitis (0.9% in the 90 mg group and 1.8% in the 90 → 180 mg group) and pneumonia (1.8% in the 90 → 180 mg group only).

In ALTA, 14% of patients required a dose reduction due to adverse reactions (7.3% in the 90 mg group and 20% in the 90 → 180 mg group). The most common adverse reaction that led to dose reduction was increased creatine phosphokinase for both regimens (1.8% in the 90 mg group and 4.5% in the 90 → 180 mg group).

Table 3 and Table 4 summarize the common adverse reactions and laboratory abnormalities observed in ALTA.

**Table 3: Adverse Reactions in ≥ 10 % (All Grades\*) or ≥ 2% (Grades 3-4) of Patients by Dose Group in ALTA (N=219)**

Adverse Reactions	90 mg once daily N = 109		90 → 180 mg once daily N = 110	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Gastrointestinal Disorders</b>				
Nausea	33	0.9	40	0.9
Diarrhea	19	0	38	0
Vomiting	24	1.8	23	0
Constipation	19	0.9	15	0
Abdominal Pain <sup>†</sup>	17	0	10	0
<b>General Disorders And Administration Site Conditions</b>				
Fatigue <sup>‡</sup>	29	1.8	36	0
Pyrexia	14	0	6.4	0.9
<b>Respiratory, Thoracic And Mediastinal Disorders</b>				
Cough	18	0	34	0
Dyspnea <sup>§</sup>	27	2.8	21	1.8 <sup>¶</sup>
ILD/Pneumonitis	3.7	1.8	9.1	2.7
Hypoxia	0.9	0	2.7	2.7
<b>Nervous System Disorders</b>				
Headache <sup>#</sup>	28	0	27	0.9
Peripheral Neuropathy <sup>♯</sup>	13	0.9	13	1.8
<b>Skin And Subcutaneous Tissue Disorders</b>				

Rash <sup>β</sup>	15	1.8	24	3.6
<b>Vascular Disorders</b>				
Hypertension	11	5.5	21	6.4
<b>Musculoskeletal And Connective Tissue Disorders</b>				
Muscle Spasms	12	0	17	0
Back pain	10	1.8	15	1.8
Myalgia <sup>à</sup>	9.2	0	15	0.9
Arthralgia	14	0.9	14	0
Pain in extremity	11	0	3.6	0.9
<b>Metabolism And Nutrition Disorders</b>				
Decreased Appetite	22	0.9	15	0.9
<b>Eye Disorders</b>				
Visual Disturbance <sup>è</sup>	7.3	0	10	0.9
<b>Infections</b>				
Pneumonia	4.6	2.8 <sup>¶</sup>	10	5.5 <sup>¶</sup>
<b>Psychiatric Disorders</b>				
Insomnia	11	0	7.3	0

\* Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

† Includes abdominal distension, abdominal pain, and epigastric discomfort

‡ Includes asthenia and fatigue

§ Includes dyspnea and exertional dyspnea

¶ Includes one Grade 5 event

# Includes headache and sinus headache

ⓓ Includes peripheral sensory neuropathy and paresthesia

β Includes acneiform dermatitis, exfoliative rash, rash, pruritic rash, and pustular rash

à Includes musculoskeletal pain and myalgia

è Includes diplopia, photophobia, blurred vision, reduced visual acuity, visual impairment, vitreous floaters, visual field defect, macular edema, and vitreous detachment

**Table 4: Laboratory Abnormalities in ≥20 % (All Grades <sup>\*</sup>) of Patients by Regimen in ALTA (N=219)**

Laboratory Abnormality	90 mg once daily N= 109		90 → 180 mg once daily N=110	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Chemistry</b>				
Increased aspartate aminotransferase	38	0.9	65	0
Hyperglycemia <sup>†</sup>	38	3.7	49	3.6
Increased creatine phosphokinase	27	2.8	48	12
Increased lipase	21	4.6	45	5.5
Increased alanine aminotransferase	34	0	40	2.7
Increased amylase	27	3.7	39	2.7
Increased alkaline phosphatase	15	0.9	29	0.9
Decreased phosphorous	15	1.8	23	3.6

Prolonged activated partial thromboplastin time	22	1.8	20	0.9
<b>Hematology</b>				
Anemia	23	0.9	40	0.9
Lymphopenia	19	2.8	27	4.5

\* Per CTCAE version 4.0

† Elevated blood insulin was also observed in both regimens

## 7 DRUG INTERACTIONS

### 7.1 Drugs That May Increase Brigatinib Plasma Concentrations

#### Strong CYP3A Inhibitors

Coadministration of itraconazole, a strong CYP3A inhibitor, increased brigatinib plasma concentrations and may result in increased adverse reactions [see *Clinical Pharmacology* (12.3)]. Avoid the concomitant use of strong CYP3A inhibitors with ALUNBRIG, including but not limited to certain antivirals (e.g., boceprevir, cobicistat, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir), macrolide antibiotics (e.g., clarithromycin), antifungals (e.g., itraconazole, ketoconazole, posaconazole, voriconazole), and conivaptan. Avoid grapefruit or grapefruit juice as it may also increase plasma concentrations of brigatinib [see *Clinical Pharmacology* (12.3)]. If concomitant use of a strong CYP3A inhibitor cannot be avoided, reduce the dose of ALUNBRIG by approximately 50% [see *Dosage and Administration* (2.3)].

### 7.2 Drugs That May Decrease Brigatinib Plasma Concentrations

#### Strong CYP3A Inducers

Coadministration of ALUNBRIG with rifampin, a strong CYP3A inducer, decreased brigatinib plasma concentrations and may result in decreased efficacy [see *Clinical Pharmacology* (12.3)]. Avoid the concomitant use of strong CYP3A inducers with ALUNBRIG, including but not limited to rifampin, carbamazepine, phenytoin, and St. John's Wort [see *Clinical Pharmacology* (12.3)].

### 7.3 Drugs That May Have Their Plasma Concentrations Altered by Brigatinib

#### CYP3A Substrates

Brigatinib induces CYP3A in vitro and may decrease concentrations of CYP3A substrates. Coadministration of ALUNBRIG with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and loss of efficacy of CYP3A substrates [see *Use in Specific Populations* (8.3)].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to a pregnant woman [see *Data and Clinical Pharmacology* (12.1)]. There are no clinical data on the use of ALUNBRIG in pregnant women. Administration of brigatinib to pregnant rats during the period of organogenesis resulted in dose-related skeletal anomalies at doses as low as 12.5 mg/kg/day (approximately 0.7 times the human exposure by AUC at 180 mg once daily) as well as increased post-implantation loss, malformations, and decreased fetal body weight at doses of 25 mg/kg/day (approximately 1.26 times the human exposure at 180 mg once daily) or greater. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

## Data

### *Animal Data*

In an embryo-fetal development study in which pregnant rats were administered daily doses of brigatinib during organogenesis, dose-related skeletal (incomplete ossification, small incisors) and visceral anomalies were observed at doses as low as 12.5 mg/kg/day (approximately 0.7 times the human exposure by AUC at 180 mg once daily). Malformations observed at 25 mg/kg/day (approximately 1.26 times the human AUC at 180 mg once daily) included anasarca (generalized subcutaneous edema), anophthalmia (absent eyes), forelimb hyperflexion, small, short and/or bent limbs, multiple fused ribs, bent scapulae, omphalocele (intestine protruding into umbilicus), and gastroschisis (intestines protruding through a defect in the abdominal wall) along with visceral findings of moderate bilateral dilatation of the lateral ventricles.

## **8.2 Lactation**

### Risk Summary

There are no data regarding the secretion of brigatinib in human milk or its effects on the breastfed infant or milk production. Because of the potential for adverse reactions in breastfed infants, advise lactating women not to breastfeed during treatment with ALUNBRIG and for 1 week following the final dose.

## **8.3 Females and Males of Reproductive Potential**

### Contraception

ALUNBRIG can cause fetal harm [*see Use in Specific Populations (8.1)*].

#### *Females*

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months after the final dose. Counsel patients to use a non-hormonal method of contraception since ALUNBRIG can render some hormonal contraceptives ineffective [*see Drug Interaction (7.3)*].

#### *Males*

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 3 months after the final dose [*see Nonclinical Toxicology (13.1)*].

### Infertility

Based on findings in male reproductive organs in animals, ALUNBRIG may cause reduced fertility in males [*see Nonclinical Toxicology (13.1)*].

## **8.4 Pediatric Use**

The safety and efficacy of ALUNBRIG in pediatric patients have not been established.

## **8.5 Geriatric Use**

Clinical studies of ALUNBRIG did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. Of the 222 patients in ALTA, 19.4% were 65-74 years and 4.1% were 75 years or older. No clinically relevant differences in safety or efficacy were observed between patients ≥65 years and younger patients.

## **8.6 Hepatic Impairment**

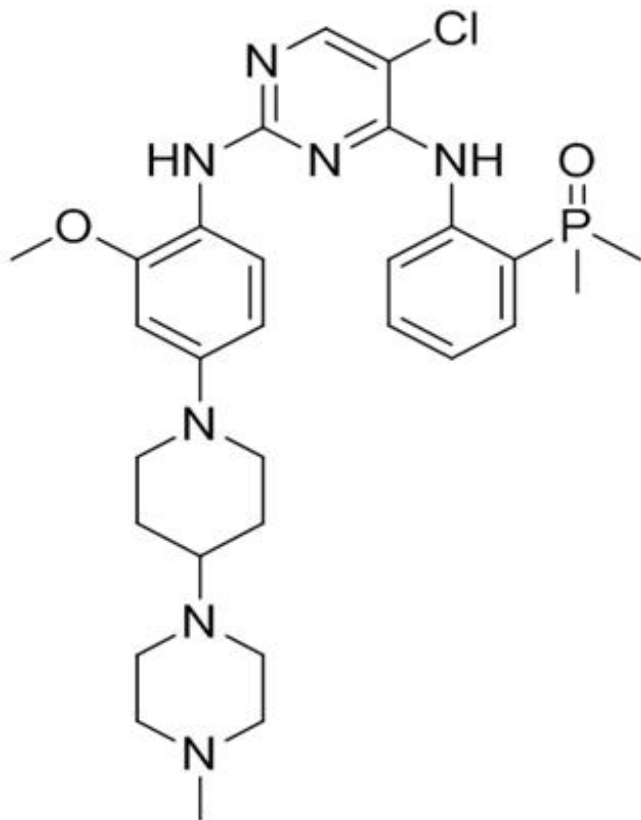
No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin within upper limit of normal [ULN] and AST greater than ULN or total bilirubin greater than 1 and up to 1.5 times ULN and any AST). The pharmacokinetics and safety of ALUNBRIG in patients with moderate or severe hepatic impairment have not been studied [see *Clinical Pharmacology* (12.3)].

### 8.7 Renal Impairment

No dose adjustment is recommended for patients with mild and moderate renal impairment [creatinine clearance ( $CL_{cr}$ ) 30 to 89 mL/min estimated by Cockcroft-Gault]. The pharmacokinetics and safety of ALUNBRIG in patients with severe renal impairment ( $CL_{cr}$  15 to 29 mL/min estimated by Cockcroft-Gault) have not been studied [see *Clinical Pharmacology* (12.3)].

## 11 DESCRIPTION

Brigatinib is a kinase inhibitor. The chemical name for brigatinib is 5-chloro-N<sup>4</sup>-[2-(dimethylphosphoryl)phenyl]-N<sup>2</sup>-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine. The molecular formula is C<sub>29</sub>H<sub>39</sub>ClN<sub>7</sub>O<sub>2</sub>P which corresponds to a formula weight of 584.10 g/mol. Brigatinib has no chiral centers. The chemical structure is shown below:



Brigatinib is an off-white to beige/tan solid. The  $pK_a$ s were determined to be:  $1.73 \pm 0.02$  (base),  $3.65 \pm 0.01$  (base),  $4.72 \pm 0.01$  (base), and  $8.04 \pm 0.01$  (base).

ALUNBRIG is supplied for oral use as film-coated tablets containing 30 mg or 90 mg of brigatinib and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (Type A), magnesium stearate, and hydrophobic colloidal silica. The tablet coating consists of talc, polyethylene glycol, polyvinyl alcohol, and titanium dioxide.

## 12 CLINICAL PHARMACOLOGY

## 12.1 Mechanism of Action

Brigatinib is a tyrosine kinase inhibitor with in vitro activity at clinically achievable concentrations against multiple kinases including ALK, ROS1, insulin-like growth factor-1 receptor (IGF-1R), and FLT-3 as well as EGFR deletion and point mutations. Brigatinib inhibited autophosphorylation of ALK and ALK-mediated phosphorylation of the downstream signaling proteins STAT3, AKT, ERK1/2, and S6 in in vitro and in vivo assays. Brigatinib also inhibited the in vitro proliferation of cell lines expressing EML4-ALK and NPM-ALK fusion proteins and demonstrated dose-dependent inhibition of EML4-ALK-positive NSCLC xenograft growth in mice.

At clinically achievable concentrations ( $\leq 500$  nM), brigatinib inhibited the in vitro viability of cells expressing EML4-ALK and 17 mutant forms associated with resistance to ALK inhibitors including crizotinib, as well as EGFR-Del (E746-A750), ROS1-L2026M, FLT3-F691L, and FLT3-D835Y. Brigatinib exhibited in vivo anti-tumor activity against 4 mutant forms of EML4-ALK, including G1202R and L1196M mutants identified in NSCLC tumors in patients who have progressed on crizotinib. Brigatinib also reduced tumor burden and prolonged survival in mice implanted intracranially with an ALK-driven tumor cell line.

## 12.2 Pharmacodynamics

Brigatinib exposure-response relationships and the time course of the pharmacodynamic response are unknown.

### Cardiac Electrophysiology

The QT interval prolongation potential of ALUNBRIG was assessed in 123 patients following once daily ALUNBRIG doses of 30 mg ( $1/6^{\text{th}}$  of the approved 180 mg dose) to 240 mg (1.3 times the approved 180 mg dose). ALUNBRIG did not prolong the QT interval to a clinically relevant extent.

## 12.3 Pharmacokinetics

The geometric mean (CV%) steady-state maximum concentration ( $C_{\text{max}}$ ) of brigatinib at ALUNBRIG doses of 90 mg and 180 mg once daily was 552 (65%) ng/mL and 1452 (60%) ng/mL, respectively, and the corresponding area under the concentration-time curve ( $AUC_{0-T_{\text{au}}}$ ) was 8165 (57%) ng·h/mL and 20276 (56%) ng·h/mL. After a single dose and repeat dosing of ALUNBRIG, systemic exposure of brigatinib was dose proportional over the dose range of 60 mg (0.3 times the approved 180 mg dose) to 240 mg (1.3 times the approved 180 mg dose) once daily. The mean accumulation ratio after repeat dosing was 1.9 to 2.4.

### Absorption

Following administration of single oral doses of ALUNBRIG of 30 to 240 mg, the median time to peak concentration ( $T_{\text{max}}$ ) ranged from 1 to 4 hours.

### *Effect of Food*

Brigatinib  $C_{\text{max}}$  was reduced by 13% with no effect on AUC in healthy subjects administered ALUNBRIG after a high fat meal (approximately 920 calories, 58 grams carbohydrate, 59 grams fat and 40 grams protein) compared to the  $C_{\text{max}}$  and AUC after overnight fasting.

### Distribution

Brigatinib is 66% bound to human plasma proteins and the binding is not concentration-dependent in vitro. The blood-to-plasma concentration ratio is 0.69. Following oral administration of ALUNBRIG 180 mg once daily, the mean apparent volume of distribution ( $V_z/F$ ) of brigatinib at steady-state was 153 L.

### Elimination

Following oral administration of ALUNBRIG 180 mg once daily, the mean apparent oral clearance ( $CL/F$ ) of brigatinib at steady-state is 12.7 L/h and the mean plasma elimination half-life is 25 hours.

## *Metabolism*

Brigatinib is primarily metabolized by CYP2C8 and CYP3A4 in vitro. Following oral administration of a single 180 mg dose of radiolabeled brigatinib to healthy subjects, N-demethylation and cysteine conjugation were the two major metabolic pathways. Unchanged brigatinib (92%) and its primary metabolite, AP26123 (3.5%), were the major circulating radioactive components. The steady-state AUC of AP26123 was less than 10% of AUC of brigatinib exposure in patients. The metabolite, AP26123, inhibited ALK with approximately 3-fold lower potency than brigatinib in vitro.

## *Excretion*

Following oral administration of a single 180 mg dose of radiolabeled brigatinib to healthy subjects, 65% of the administered dose was recovered in feces and 25% of the administered dose was recovered in urine. Unchanged brigatinib represented 41% and 86% of the total radioactivity in feces and urine, respectively.

## Specific Populations

Age, race, sex, body weight, and albumin concentration have no clinically meaningful effect on the pharmacokinetics of brigatinib.

## *Hepatic Impairment*

As hepatic elimination is a major route of excretion for brigatinib, hepatic impairment may result in increased plasma brigatinib concentrations. Based on a population pharmacokinetic analysis, brigatinib exposures were similar between 49 subjects with mild hepatic impairment (total bilirubin within upper limit of normal [ULN] and AST greater than ULN or total bilirubin greater than 1 and up to 1.5 times ULN and any AST) and 377 subjects with normal hepatic function (total bilirubin and AST within ULN). The pharmacokinetics of brigatinib in patients with moderate (total bilirubin greater than 1.5 and up to 3.0 times ULN and any AST) to severe (total bilirubin greater than 3.0 times ULN and any AST) hepatic impairment has not been studied.

## *Renal Impairment*

Based on a population pharmacokinetic analysis, brigatinib exposures were similar among 125 subjects with mild renal impairment ( $CL_{cr}$  60 to less than 90 mL/min), 34 subjects with moderate renal impairment ( $CL_{cr}$  30 to less than 60 mL/min) and 270 subjects with normal renal function ( $CL_{cr}$  greater than or equal to 90 mL/min), suggesting that no dose adjustment is necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment ( $CL_{cr}$  less than 30 mL/min) were not included in clinical trials.

## Drug Interactions

### *Effects of Other Drugs on Brigatinib*

**Strong CYP3A Inhibitors:** Coadministration of 200 mg twice daily doses of itraconazole (a strong CYP3A inhibitor) with a single 90 mg dose of ALUNBRIG increased brigatinib  $C_{max}$  by 21% and  $AUC_{0-INF}$  by 101%, relative to a 90 mg dose of ALUNBRIG administered alone [see *Dosage and Administration (2.3) and Drug Interactions (7.1)*].

**Strong CYP2C8 Inhibitors:** Coadministration of 600 mg twice daily doses of gemfibrozil (a strong CYP2C8 inhibitor) with a single 90 mg dose of ALUNBRIG decreased brigatinib  $C_{max}$  by 41% and  $AUC_{0-INF}$  by 12%, relative to a 90 mg dose of ALUNBRIG administered alone. The effect of gemfibrozil on the pharmacokinetics of brigatinib is not clinically meaningful and the underlying mechanism for the decreased exposure of brigatinib is unknown.

**Strong CYP3A Inducers:** Coadministration of 600 mg daily doses of rifampin (a strong CYP3A inducer) with a single 180 mg dose of ALUNBRIG decreased brigatinib  $C_{max}$  by 60% and  $AUC_{0-INF}$  by 80%, relative to a 180 mg dose of ALUNBRIG administered alone [see *Drug Interactions (7.2)*].

**P-gp and BCRP Inhibitors:** In vitro studies suggest that brigatinib is a substrate of the efflux transporters

P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Given that brigatinib exhibits high solubility and high permeability in vitro, P-gp and BCRP inhibitors are unlikely to increase plasma concentrations of brigatinib.

*Other Transporters:* Brigatinib is not a substrate of organic anion transporting polypeptide (OATP1B1, OATP1B3), organic anion transporter (OAT1, OAT3), organic cation transporter (OCT1, OCT2), multidrug and toxin extrusion protein (MATE1, MATE2K), or bile salt export pump (BSEP).

#### *Effects of Brigatinib on Other Drugs*

*Transporter Substrates:* Brigatinib is an inhibitor of P-gp, BCRP, OCT1, MATE1, and MATE2K in vitro. Therefore, brigatinib may have the potential to increase concentrations of coadministered substrates of these transporters. Brigatinib at clinically relevant concentrations did not inhibit OATP1B1, OATP1B3, OAT1, OAT3, OCT2 or BSEP.

*CYP Substrates:* Brigatinib and its primary metabolite, AP26123, did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 at clinically relevant concentrations.

Brigatinib, at clinically relevant plasma concentrations, induced CYP3A via activation of the pregnane X receptor (PXR). Brigatinib may also induce CYP2C enzymes via the same mechanism at clinically relevant concentrations.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Carcinogenicity studies have not been performed with brigatinib.

Treatment with brigatinib resulted in chromosomal damage in an in vivo mammalian erythrocyte micronucleus in the rat, but was not mutagenic in the Ames or in vitro mammalian chromosome aberration tests.

Dedicated animal fertility studies were not conducted with brigatinib. Testicular toxicity was observed in repeat-dose animal studies at doses resulting in exposure as low as 0.2 times the exposure in patients at the 180 mg dose. In rats, findings included lower weight of testes, seminal vesicles and prostate gland, and testicular tubular degeneration; these effects were not reversible during the 2-month recovery period. In monkeys, findings included reduced size of testes along with microscopic evidence of hypospermatogenesis; these effects were reversible during the recovery period.

## **14 CLINICAL STUDIES**

The efficacy of ALUNBRIG was demonstrated in a two-arm, open-label, multicenter trial (ALTA, NCT02094573) in adult patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) who had progressed on crizotinib. The study required patients to have a documented ALK rearrangement based on an FDA-approved test or a different test with adequate archival tissue to confirm ALK arrangement by the Vysis<sup>®</sup> ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit test. Key eligibility criteria included an ECOG Performance Status of 0-2 and progression on crizotinib. Neurologically stable patients with central nervous system (CNS) metastases were permitted to enroll. Patients with a history of interstitial lung disease or drug-related pneumonitis or who had received crizotinib within 3 days of the first dose of brigatinib were excluded. The major efficacy outcome measure was confirmed overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by an Independent Review Committee (IRC). Additional efficacy outcome measures included Investigator-assessed ORR, duration of response (DOR), intracranial ORR, and intracranial DOR.

A total of 222 patients were randomized to receive ALUNBRIG either 90 mg once daily (90 mg arm; n=112) or 180 mg once daily following a 7-day lead-in at 90 mg once daily (90 → 180 mg arm; n=110).



Randomization was stratified by brain metastases (present versus absent) and best prior response to crizotinib (complete or partial response versus any other response/unevaluable).

Baseline demographic characteristics of the overall study population were: median age 54 years (range 18 to 82, 23% 65 and over), 67% White and 31% Asian, 57% female, 36% ECOG PS 0 and 57% ECOG PS 1, and 95% never or former smokers. The disease characteristics of the overall study population were: Stage IV disease in 98%, adenocarcinoma histology in 97%, prior systemic chemotherapy in 74%, metastatic disease to the brain in 69% (61% had received prior radiation to the brain), bone metastases in 39%, and liver metastases in 26% of patients. Sixty-four percent of patients had an objective response to prior crizotinib.

The median duration of follow-up was 8 months (range: 0.1-20.2). Efficacy results from ALTA are summarized in Table 5.

**Table 5: ALTA Efficacy Results**

Efficacy parameter	IRC Assessment		Investigator Assessment	
	90 mg once daily (N=112)	90 → 180 mg once daily (N=110)	90 mg once daily (N=112)	90 → 180 mg once daily (N=110)
Overall Response Rate (95% CI)	48% (39-58)	53% (43-62)	45% (35-54)	54% (44-63)
Complete Response, n (%)	4 (3.6%)	5 (4.5%)	1 (0.9%)	4 (3.6%)
Partial Response, n (%)	50 (45%)	53 (48%)	49 (44%)	55 (50%)
Duration of Response, median in months (95% CI)	13.8 (7.4-NE)	13.8 (9.3-NE)	13.8 (5.6-13.8)	11.1 (9.2-13.8)

CI = Confidence Interval; NE = Not Estimable

IRC assessment of intracranial ORR and intracranial DOR according to RECIST v1.1 in the subgroup of 44 patients with measurable brain metastases ( $\geq 10$  mm in longest diameter) at baseline are summarized in Table 6. Duration of intracranial response was measured from date of first intracranial response until intracranial disease progression (new lesions, intracranial target lesion diameter growth  $\geq 20\%$  from nadir, or unequivocal progression of intracranial non-target lesions) or death.

**Table 6: Intracranial Objective Response in Patients with Measurable Brain Metastases in ALTA**

Efficacy parameter	IRC Assessment	
	90 mg once daily (N=26)	90 → 180 mg once daily (N=18)
Intracranial Overall Response Rate, (95 % CI)	42% (23-63)	67% (41-87)
Complete Response, n (%)	2 (7.7%)	0
Partial Response, n (%)	9 (35%)	12 (67%)
Duration of Intracranial Response, median (months) (range)	NE (1.9+ - 9.2+)	5.6 (1.9+ - 9.2+)

CI = Confidence Interval; NE = Not Estimable

Among the 23 patients who exhibited an intracranial response, 78% of patients in the 90 mg arm and 68% of patients in the 90 → 180 mg arm maintained a response for at least 4 months.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

30 mg tablets: round, white to off-white film-coated tablet with "U3" debossed on one side and plain on the other side; available in:

Bottles of 21 tablets	NDC 76189-113-21
Bottles of 180 tablets	NDC 76189-113-18

90 mg tablets: oval, white to off-white film-coated tablet with "U7" debossed on one side and plain on the other side; available in:

Bottles of 7 tablets	NDC 76189-119-07
Bottles of 30 tablets	NDC 76189-119-30

Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursion permitted between 15°C to 30°C (59°F to 86°F) (see USP).

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Inform patients of the following:

### Interstitial Lung Disease (ILD)/Pneumonitis

Inform patients of the symptoms and risks of serious pulmonary adverse reactions such as ILD/pneumonitis. Advise patients to immediately report any new or worsening respiratory symptoms [see *Warnings and Precautions* (5.1)].

### Hypertension

Advise patients of risks of hypertension and to promptly report signs or symptoms of hypertension [see *Warnings and Precautions* (5.2)].

### Bradycardia

Advise patients to report any symptoms of bradycardia and to inform their healthcare provider about the use of heart and blood pressure medications [see *Warnings and Precautions* (5.3)].

### Visual Disturbance

Advise patients to inform their healthcare provider of any new or worsening vision symptoms [see *Warnings and Precautions* (5.4)].

### Creatine Phosphokinase (CPK) Elevation

Inform patients of the signs and symptoms of creatinine phosphokinase (CPK) elevation and the need for monitoring during treatment. Advise patients to inform their healthcare provider of any new or worsening symptoms of unexplained muscle pain, tenderness, or weakness [see *Warnings and Precautions* (5.5)].

### Pancreatic Enzyme Elevation

Inform patients of the signs and symptoms of pancreatitis and the need to monitor for amylase and lipase elevations during treatment [see *Warnings and Precautions* (5.6)].

### Hyperglycemia

Inform patients of the risks of new or worsening hyperglycemia and the need to periodically monitor glucose levels. Advise patients with diabetes mellitus or glucose intolerance that anti-hyperglycemic

medications may need to be adjusted during treatment with ALUNBRIG [see *Warnings and Precautions* (5.7)].

### Females and Males of Reproductive Potential

#### *Embryo-Fetal Toxicity*

Advise females and males of reproductive potential that ALUNBRIG can cause fetal harm [see *Warnings and Precautions* (5.8) and *Use in Specific Populations* (8.1)].

- Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy and to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months after the final dose [see *Use in Specific Populations* (8.3)].
- Advise males with female partners of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 3 months after the final dose [see *Use in Specific Populations* (8.3)].

#### *Lactation*

Advise females not to breastfeed during treatment with ALUNBRIG and for at least 1 week following the final dose [see *Use in Specific Populations* (8.2)].

#### *Infertility*

Advise males of reproductive potential of the potential for reduced fertility from ALUNBRIG [see *Use in Specific Populations* (8.3) and *Nonclinical Toxicology* (13.1)].

### Drug Interactions

Advise patients to inform their health care provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid grapefruit or grapefruit juice while taking ALUNBRIG [see *Drug Interactions* (7)].

### Dosing and Administration

Instruct patients to start with 90 mg of ALUNBRIG once daily for the first 7 days and if tolerated, increase the dose to 180 mg once daily. Advise patients to take ALUNBRIG with or without food [see *Dosage and Administration* (2.1)].

### Missed Dose

Advise patients that if a dose of ALUNBRIG is missed or if the patient vomits after taking a dose of ALUNBRIG, not to take an extra dose, but to take the next dose at the regular time [see *Dosage and Administration* (2.1)].

Manufactured for:

ARIAD Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited  
Cambridge, MA

<p><b>PATIENT INFORMATION</b> <b>ALUNBRIG (uh-lun-brig)</b> <b>(brigatinib)</b> <b>tablets</b></p>
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<p><b>What is the most important information I should know about ALUNBRIG?</b></p>
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<p><b>ALUNBRIG can cause serious side effects, including:</b></p>
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- |  |
|--|
| <ul style="list-style-type: none"><li>• <b>Lung problems. ALUNBRIG may cause severe or life-threatening swelling (inflammation) of the lungs any time during treatment, and can lead to death.</b> These lung problems happen <b>especially within the first week of treatment</b> with ALUNBRIG. Symptoms may be similar to those symptoms from lung cancer. Tell your healthcare provider right away if you have any new or worsening symptoms, including:</li></ul> |
|--|

- trouble breathing or shortness of breath
- chest pain
- cough with or without mucous
- fever

- **High blood pressure (hypertension).** ALUNBRIG may cause high blood pressure. Your healthcare provider will check your blood pressure before starting and during treatment with ALUNBRIG. Tell your healthcare provider right away if you get headaches, dizziness, blurred vision, chest pain or shortness of breath.
- **Slow heart rate (bradycardia).** ALUNBRIG may cause very slow heartbeats that can be severe. Your healthcare provider will check your heart rate during treatment with ALUNBRIG. Tell your healthcare provider right away if you feel dizzy, lightheaded, or faint during treatment with ALUNBRIG. Tell your healthcare provider if you start to take or have any changes in heart or blood pressure medicines.
- **Vision problems.** ALUNBRIG may cause vision problems. Your healthcare provider may stop ALUNBRIG and refer you to an eye specialist if you develop severe vision problems during treatment with ALUNBRIG. Tell your healthcare provider right away if you have any loss of vision or any change in vision, including:
  - double vision
  - seeing flashes of light
  - blurry vision
  - light hurting your eyes
  - new or increased floaters
- **Muscle pain, tenderness, and weakness (myalgia).** ALUNBRIG may increase the level of an enzyme in your blood called creatine phosphokinase (CPK), which may be a sign of muscle damage. Your healthcare provider will do blood tests to check your blood levels of CPK during treatment with ALUNBRIG. Tell your healthcare provider right away if you get new or worsening signs and symptoms of muscle problems, including unexplained muscle pain or muscle pain that does not go away, tenderness, or weakness.
- **Inflammation of the pancreas (pancreatitis).** ALUNBRIG may increase enzymes in your blood called amylase and lipase, which may be a sign of pancreatitis. Your healthcare provider will do blood tests to check your pancreatic enzyme blood levels during treatment with ALUNBRIG. Tell your healthcare provider right away if you get new or worsening signs and symptoms of pancreatitis, including upper abdominal pain that may spread to the back and get worse with eating, weight loss, or nausea.
- **High blood sugar (hyperglycemia).** ALUNBRIG may increase your blood sugar levels. Your healthcare provider will do blood tests to check your blood sugar levels before starting and during treatment with ALUNBRIG. Your healthcare provider may need to start or change your blood sugar medicine to control your blood sugar levels. Tell your healthcare provider right away if you get new or worsening signs and symptoms of hyperglycemia, including:
  - feeling very thirsty
  - needing to urinate more than usual
  - feeling very hungry
  - feeling sick to your stomach
  - feeling weak or tired
  - feeling confused

See "What are the possible side effects of ALUNBRIG?" for information about side effects.

#### What is ALUNBRIG?

ALUNBRIG is a prescription medicine used to treat people with non-small cell lung cancer (NSCLC):

- that has a certain type of abnormal anaplastic lymphoma kinase (ALK) gene, **and**
- that has spread to other parts of your body, **and**
- who have taken the medicine crizotinib, but their NSCLC worsened or they cannot tolerate taking

crizotinib.

It is not known if ALUNBRIG is safe and effective in children.

**Before you take ALUNBRIG, tell your healthcare provider about all of your medical conditions, including if you:**

- have lung or breathing problems
- have high blood pressure
- have a slow heartbeat
- have any vision problems
- have or have had pancreatitis
- have diabetes mellitus or glucose intolerance
- are pregnant or plan to become pregnant. ALUNBRIG can harm your unborn baby. Tell your healthcare provider right away if you become pregnant during treatment with ALUNBRIG or think you may be pregnant.
  - **Females** who are able to become pregnant should use effective non-hormonal birth control during treatment with ALUNBRIG and for at least 4 months after the final dose of ALUNBRIG. Birth control pills (oral contraceptives) and other hormonal forms of birth control may not be effective if used during treatment with ALUNBRIG. Talk to your healthcare provider about birth control choices that are right for you during treatment with ALUNBRIG.
  - **Males** who have female partners that are able to become pregnant should use effective birth control during treatment with ALUNBRIG and for at least 3 months after the final dose of ALUNBRIG.
- are breastfeeding or plan to breastfeed. It is not known if ALUNBRIG passes into your breast milk. Do not breastfeed during treatment with ALUNBRIG and for 1 week after the final dose of ALUNBRIG.

**Tell your healthcare provider about all the medicines you take,** including prescription medicines, over-the-counter medicines, vitamins, or herbal supplements.

**How should I take ALUNBRIG?**

- Take ALUNBRIG exactly as your healthcare provider tells you to take it. Do not change your dose or stop taking ALUNBRIG unless your healthcare provider tells you to.
- Your healthcare provider will start you on a low dose (90 mg) of ALUNBRIG for the first 7 days of treatment. If you tolerate this dose of ALUNBRIG well, your healthcare provider may increase your dose after the first 7 days of treatment.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with ALUNBRIG if you have side effects.
- Take ALUNBRIG 1 time each day.
- Take ALUNBRIG with or without food.
- Swallow ALUNBRIG tablets whole. Do not crush or chew tablets.
- If you miss a dose of ALUNBRIG, do not take the missed dose. Take your next dose at your regular time.
- If you vomit after taking a dose of ALUNBRIG, do not take an extra dose. Take your next dose at your regular time.

**What should I avoid while taking ALUNBRIG?**

- Avoid eating grapefruit or drinking grapefruit juice during treatment with ALUNBRIG. Grapefruit may increase the amount of ALUNBRIG in your blood.

**What are the possible side effects of ALUNBRIG?**

**ALUNBRIG may cause serious side effects, including:**

- See "What is the most important information I should know about ALUNBRIG?"

**The most common side effects of ALUNBRIG include:**

- nausea
- fatigue
- headache
- diarrhea
- cough

ALUNBRIG may cause fertility problems in males. This may affect your ability to father a child. Talk to your healthcare provider if you have concerns about fertility.

These are not all of the possible side effects of ALUNBRIG. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store ALUNBRIG?**

- Store ALUNBRIG at room temperature 20°C to 25°C (68°F to 77°F).

**Keep ALUNBRIG and all medicines out of the reach of children.****General information about the safe and effective use of ALUNBRIG.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information. Do not use ALUNBRIG for a condition for which it was not prescribed. Do not give ALUNBRIG to other people, even if they have the same symptoms you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about ALUNBRIG that is written for health professionals.

**What are the ingredients in ALUNBRIG?**

**Active ingredient:** brigatinib

**Inactive ingredients:** lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (Type A), magnesium stearate, and hydrophobic colloidal silica. The tablet coating consists of talc, polyethylene glycol, polyvinyl alcohol, and titanium dioxide.

Manufactured for: ARIAD Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA

For more information, go to [www.alunbrig.com](http://www.alunbrig.com) or call 1-844-217-6468.

This Patient Information has been approved by the U.S. Food and Drug Administration

Issued: April 2017

**PRINCIPAL DISPLAY PANEL - 30 mg Tablet Bottle Label**

NDC 76189-113-18


**Alunbrig™**  
**(brigatinib) tablets**

**30 mg**  
**Rx Only**

Each tablet contains 30 mg brigatinib

180 Tablets

ARIAD®



00376189113184

Store at controlled room temperature 68° to 77°F (20° to 25°C); excursion permitted between 59° to 86°F (15°C to 30°C) (see USP).

**Usual Dose:**  
See prescribing information.

**KEEP AWAY FROM CHILDREN**

LA00311A


NDC 76189-113-18

**Alunbrig™**  
(brigatinib) tablets

**30 mg** Rx Only

Each tablet contains 30 mg brigatinib

180 Tablets



Mfg. by Penn Pharmaceutical Services Ltd.  
23/24 Tafarnaubach Industrial Estate,  
Gwent, UK NP22 3AA for  
ARIAD Pharmaceuticals, Inc.

Lot  
Expiry

ALUNBRIG

brigatinib tablet, coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:76189-113
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name		Strength
Brigatinib (UNII: HYW8DB273J) (Brigatinib - UNII:HYW8DB273J)		30 mg

Inactive Ingredients	
Ingredient Name	
SILICA DIMETHYL SILYLATE (UNII: EU2PSP0G0W)	
Lactose Monohydrate (UNII: EWQ57Q8I5X)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
POLYVINYL ALCOHOL, UNSPECIFIED (UNII: 532B59J990)	
WATER (UNII: 059QF0K00R)	

Product Characteristics			
Color	WHITE	Score	no score
Shape	OVAL	Size	7mm
Flavor		Imprint Code	U3
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date

<b>1</b>	NDC:76 189-113-21	21 in 1 BOTTLE; Type 0: Not a Combination Product	04/28/2017	12/12/2020
<b>2</b>	NDC:76 189-113-18	180 in 1 BOTTLE; Type 0: Not a Combination Product	04/28/2017	12/12/2020
<b>Marketing Information</b>				
<b>Marketing Category</b>		<b>Application Number or Monograph Citation</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>
NDA		NDA208772	04/28/2017	12/12/2020

**Labeler** - ARIAD Pharmaceuticals Inc. (786227231)

**Registrant** - PENN PHARMACEUTICAL SERVICES LTD (226277259)

<b>Establishment</b>			
<b>Name</b>	<b>Address</b>	<b>ID/FEI</b>	<b>Business Operations</b>
ARIAD Pharmaceuticals Inc.		786227231	MANUFACTURE(76 189-113) , ANALYSIS(76 189-113) , PACK(76 189-113)

Revised: 12/2018

ARIAD Pharmaceuticals Inc.